=> d 1-23 all

L3 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN [illegible] HCAPLUS
TI Hydroxyurea and ***trimidox*** enhance the radiation effect in human pancreatic adenocarcinoma cells
AU Lyden, D.; Ahmed, N.; Hassan, H. T.
CS Division of Biomedical Sciences, School of Health Sciences, University of Wolverhampton, Wolverhampton, WV1 1DJ, UK
SO Anticancer Res. (2000), 20(1A), 133-139
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
CC 8 (Radiation Biochemistry)
AB BACKGROUND: Pancreatic cancer remains the most lethal of all common human malignancies with a 5-yr survival rate of lower than 5%. Adjuvant and neoadjuvant preoperative and postoperative chemo-radiotherapy using 5-fluorouracil, have reduced local relapse rate and slightly increased the median survival. Testing new and more potent radiation-sensitizing drugs in human pancreatic cancer cells can provide the basis for a more effective chemo-radiation regimen and may consequently improve treatment outcome. MATERIALS & METHODS: The present study was performed to evaluate the efficacy of two potent ribonucleotide reductase (RR) inhibitors: hydroxyurea and ***trimidox*** in radio-sensitizing Panc-1 human pancreatic cancer cells in an attempt to identify a more effective chemo-radiotherapy regimen with minimal side effects. RESULTS: Treatment of Panc-1 cells with hydroxyurea or ***trimidox*** alone for 2 h was assocd. with a dose-dependent decrease in their cloning efficacy to similar extent. The IC50 of ***trimidox*** , hydroxyurea or radiation alone were 2.5 + 0.3 .mu.M, 39.0 + 0.4 .mu.M and 3.2 + 0.2 Gy, resp. Treatment with 39.0 microM non-cytotoxic IC50 dose of hydroxyurea for two hours before or immediately after radiation reduced the IC50 of radiation to only 1.1 + 0.14 or 1.0 + 0.1 Gy, resp. Treatment with 2.5 microM non-cytotoxic IC50 dose of ***trimidox*** for two hours before or immediately after radiation reduced the IC50 of radiation to only 1.2 + 0.16 or 1.4 + 0.12 Gy, resp. The mean radiation enhancement ratios were 2.9 and 3.2 for hydroxyurea before and immediately after radiation. The greater radio-sensitizing effect of hydroxyurea compared to ***trimidox*** or gemcitabine could be due to its unique double action by synchronising the cancer cells into the radiosensitive G1/S border and inhibiting DNA damage repair. CONCLUSIONS: The present study demonstrates the superiority of hydroxyurea at non-cytotoxic doses compared to the other two recent RR inhibitors: gemcitabine and ***trimidox*** in radio-sensitizing human pancreatic cancer cells. Hydroxyurea combined with radiation has significantly improved progression-free survival of advanced cervical cancer and glioblastoma patients and showed clin. benefit in combination with other chemotherapy drugs in advanced pancreatic cancer. The present results suggest the clin. use of hydroxyurea as a radiosensitizer in both pre- and post-operative chemo-radiotherapy in pancreatic cancer patients. Given the demonstrated potent radio-sensitizing effect of hydroxyurea at non-cytotoxic doses when administered before or immediately after radiation and its low clin. toxicity, it sould be feasible to administer hydroxyurea both before and after radiation in pancreatic cancer patients.
RE.CNT 35
RE

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L3 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:244031 HCAPLUS
TI Enhancement of hemoglobin and F-cell production by targeting growth inhibition and differentiation of K562 cells with ribonucleotide reductase inhibitors (didox and ***trimidox***) in combination with streptozotocin
AU Iyamu, W. E.; Adunyah, S. E.; Fasold, H.; Horiuchi, K.; Elford, H. L.; Asakura, T.; Turner, E. A.
CS Comprehensive Sickle Cell Center, Meharry Medical College, Nashville, TN, USA
SO Am. J. Hematol. (2000), 63(4), 176-183
CODEN: AJHEDD; ISSN: 0361-8609
PB Wiley-Liss, Inc.
DT Journal
LA English
CC 1 (Pharmacology)
AB Upon appropriate drug treatment, the human erythroleukemic K562 cells have been shown to produce Hb and F-cells. Fetal Hb (Hb F) inhibits the polymn. events of sickle Hb (Hb S), thereby ameliorating the clin. symptoms of sickle cell disease. Ribonucleotide reductase inhibitors (RRIs) have been shown to inhibit the growth of myeloid leukemia cells leading to the prodn. of Hb F upon differentiation. Of the RRIs currently in use, hydroxyurea is the most effective agent for Hb F induction. We have examd. the capacity of two novel RRIs, didox (DI) and ***trimidox*** (TRI), in combination with streptozotocin (STZ), to induce Hb and F-cell prodn. The K562 cells were cultured with different concns. of didox-STZ or ***trimidox*** -STZ at a fixed molar ratio of 3:1 and 1:5 for 96 h, resp. At pre-detd. time intervals, aliquots of cells were obtained and total Hb (benzidine pos.) levels, no. of F-cells, and Hb F were detd. by the differential staining technique, fetal Hb assay kit, and fluorescence cytometry resp. The effect of combined drug treatment on the growth of K562 cells was examd. by isobologram anal. Our results indicate that a synergistic growth-inhibitory differentiation effect occurred when didox or ***trimidox*** was used in combination with STZ on K562 cells. There was an increase in the no. of both benzidine-pos. normoblasts and F-cells, accompanied by morphol. appearances typical of erythroid maturation. On day 4, the no. of benzidine-pos. cells showed a 6-9-fold increase and the no. of F-cells was between 2.5- and 5.7-fold higher than the resp. controls. Based upon these results, treatment with a ribonucleotide reductase inhibitor, such as didox or ***trimidox*** , in combination with STZ, might offer an addnl. promising option in sickle cell disease therapy.
RE.CNT 32
RE

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L3 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:209828 HCAPLUS
DN 132:246339
TI Antiviral drug compositions containing lithium salts

IN Gallicchio, Vincent S.
PA University of Kentucky Research Foundation, USA
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
IC [illegible]
ICS [illegible]
CC 1-5 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO [illegible] A1 [illegible] WO 1999-US[illegible] [illegible]
W: CA
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AB A compn. and a pharmaceutical compn. of lithium .gamma.-linolenate and an antiviral or antibiotic are provided. Also provided is a method of treating acquired immune deficiency syndrome (AIDS) with lithium .gamma.-linolenate and zidovudine. Further provided is a method of decreasing the toxicity of an antiviral or antibiotic including administering a toxicity-reducing effective amt. of a compn. of a lithium salt with an antiviral or antibiotic.

ST lithium salt antiviral antibiotic toxicity redn; linolenate gamma lithium antiviral AIDS; zidovudine lithium gamma linolenate AIDS

IT Antiviral agents
Bone marrow
Drug delivery systems
Eosinophil
Hematocrit
Hematopoiesis
Human immunodeficiency virus
Immunostimulants
Leukocyte
Lymphocyte
Megakaryocyte
Murine immunodeficiency virus
Neutrophil
Platelet (blood)
Spleen
(antiviral drug compns. contg. lithium salts)

IT Nucleoside analogs
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral drug compns. contg. lithium salts)

IT Toxicity
(drug; antiviral drug compns. contg. lithium salts)

IT Hematopoietic precursor cell
(erythroid burst-forming; antiviral drug compns. contg. lithium salts)

IT Hematopoietic precursor cell
(erythroid; antiviral drug compns. contg. lithium salts)

IT Hematopoietic precursor cell
(granulocyte-macrophage colony-forming; antiviral drug compns. contg. lithium salts)

IT AIDS (disease)
(murine leukemia virus-induced AIDS-like syndrome; antiviral drug compns. contg. lithium salts)

IT Hematopoietic precursor cell
(myeloid; antiviral drug compns. contg. lithium salts)

IT Megakaryocyte
(promegakaryocyte; antiviral drug compns. contg. lithium salts)

IT 50-18-0, Cyclophosphamide 127-07-1, Hydroxyurea 3056-17-5, d4T 7481-89-2, DdC 9042-14-2, Dextran sulfate 30516-87-1, Zidovudine 69655-05-6, DdI 69839-83-4, Didox 95933-74-7, ***Trimidox*** 129618-40-2, Nevirapine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral drug compns. contg. lithium salts)

IT 554-13-2, Lithium carbonate 919-16-4, Lithium citrate 7439-93-2D, Lithium, salts 7447-41-8, Lithium chloride, biological studies 10377-48-7, Lithium sulfate 66004-77-1 93858-64-1 93939-77-6 122051-95-0, Lithium .gamma.-linolenate 122406-02-4
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral drug compns. contg. lithium salts)

IT 9001-92-7, Protease 9040-57-7, Ribonucleotide reductase 9068-38-6, Reverse transcriptase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; antiviral drug compns. contg. lithium salts)

RE.CNT 7
RE

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L3 ANSWER 4 OF 33 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:[illegible] HCAPLUS
DN 132:[illegible]
TI In vivo and in vitro comparison of the short-term hematopoietic toxicity between hydroxyurea and ***trimidox*** or didox, novel ribonucleotide reductase inhibitors with potential anti-HIV-1 activity
AU Mayhew, Christopher N.; Phillips, Jonathan D.; Greenberg, Richard N.; Birch, Nicholas J.; Elford, Howard L.; Gallicchio, Vincent S.
CS School of Health Sciences, University of Wolverhampton, Wolverhampton, UK
SO Stem Cells (Miamisburg, Ohio) (1999), 17(6), 345-356
CODEN: STCEEJ; ISSN: 1066-5099
PB AlphaMed Press
DT Journal
LA English
CC 1-5 (Pharmacology)

AB The short-term hematopoietic toxicity of the ribonucleotide reductase inhibitor hydroxyurea (HU) was studied in mice in comparison with that of the more potent enzyme inhibitors didox (DX) and ***trimidox*** (TX). High-dose HU, DX, and TX monotherapy (500, 460, and 220 mg/kg/day, resp.) was administered by daily i.p. injection (Monday-Friday) to C57BL/6 mice for 10 wk. Effects on hematopoiesis were established by quantitating peripheral blood indexes and nos. of colony-forming units-granulocyte-macrophage (CFU-GM) and BFU-E [not defined] from bone marrow and spleen. HU rapidly induced a macrocytic hypochromic anemia and altered white blood cell kinetics, assocd. with myelosuppression, defined as reduced marrow organ cellularity and induction of splenic extramedullary hematopoiesis. Compared to HU, TX and DX induced fewer changes in peripheral blood indexes and CFU-GM and BFU-E per hematopoietic organ. In vitro human and murine marrow CFU-GM and BFU-E colony formations were assayed in the presence of increasing concns. of HU, DX, or TX (0, 1, 10, 50, 100, and 200 .mu.M). HU inhibited colony formation more than either DX or TX. These studies suggest that the novel ribonucleotide reductase inhibitors TX and DX may provide an effective alternative to HU in HIV-1 therapy because they cause less hematopoietic toxicity.

ST hematopoiesis toxicity ribonucleotide reductase inhibitor; hydroxyurea ***trimidox*** didox hematopoiesis toxicity

IT Hematopoietic precursor cell
(granulocyte-macrophage; hematopoietic toxicity of hydroxyurea, ***trimidox*** and didox, ribonucleotide reductase inhibitors)

IT Hematopoiesis
(hematopoietic toxicity of hydroxyurea, ***trimidox*** and didox, ribonucleotide reductase inhibitors)

IT Anti-AIDS agents
Human immunodeficiency virus 1
(hematopoietic toxicity of hydroxyurea, ***trimidox*** and didox, ribonucleotide reductase inhibitors with potential anti-HIV-1 activity)

IT 127-07-1, Hydroxyurea 69839-83-4, Didox 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(hematopoietic toxicity of hydroxyurea, ***trimidox*** and didox, ribonucleotide reductase inhibitors)

IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; hematopoietic toxicity of hydroxyurea, ***trimidox*** and didox, ribonucleotide reductase inhibitors)

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L3 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:511044 HCAPLUS
DN 131:139487
TI Pharmaceutical compositions comprising PEG-asparaginase for the treatment of HIV infections
IN Avramis, Vassilios I.; Cohen, Lewis
PA Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SO PCT Int. Appl., 81 pp.
 CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-50
CC 1-5 (Pharmacology)
 Section cross-reference(s): 63
FAN.CNT 1

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    PATENT NO.      KIND  DATE          APPLICATION NO.  DATE
    --------------- ----  --------      ---------------  --------
PI  WO 9939732       A1   19990812      WO 1999-US2480   19990209
        W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
           DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP,
           KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,
           NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA,
           UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
           FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
           CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    AU 9926584       A1   19990823      AU 1999-26584    19990209
PRAI US 1998-PV74066  19980209
    US 1998-74066    19980209
    WO 1999-US2480   19990209
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OS MARPAT 131:139487
AB A method of inhibiting or treating Human Immunodeficiency Virus (HIV) infection comprises administering to a patient in need thereof an effective amt. of a pharmaceutically acceptable compn. comprising a PEG-ASNase compd. and optionally at least one compd. selected from the group consisting of protease inhibitor compds., ribonucleotide reductase inhibitor compds. and HIV reverse transcriptase inhibitor compds.
ST PEG asparaginase HIV infection treatment
IT Antiviral agents
 Drug delivery systems
 Human immunodeficiency virus
 Human immunodeficiency virus 1
 (PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT Amino acids, biological studies
 RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
 (PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT Viral RNA
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
 (PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT Polyoxyalkylenes, biological studies
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (asparaginase conjugates; PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT Drug delivery systems
 (prodrugs; PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT Drug interactions
 (synergistic; PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT 127-07-1, Hydroxyurea 3056-17-5, d4T 7481-89-2, DdC 9015-68-3D, Asparaginase, PEG conjugates 25322-68-3D, PEG, asparaginase conjugates 30516-87-1, AZT 69655-05-6, DdI 69839-83-4, Didox 74140-70-5, Parabactin 95933-72-5, Amidox 95933-74-7, ***Trimidox*** 110311-27-8, Sulofenur 123318-82-1, 2-Chloro-9-(2-deoxy-2-fluoro-.beta.-D-arabinofuranosyl)adenine 127142-14-7, BW 348U87 127779-20-8, Saquinavir 130306-02-4, MDL 101731 134678-17-4, 3TC 143621-35-6, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone 144096-13-9, BILD 733 150378-17-9, Indinavir 150683-14-2, LY 295501 155213-67-5, Ritonavir 156130-57-3, LY 307703 157810-81-6, Crixivan 159989-64-7, Nelfinavir 159989-65-8, Viracept 160299-99-0, BILD 1263 161635-61-6, BILD 1357 161814-49-9, VX-478 169234-52-2, BILD 1257 173883-67-9 180100-99-6, TAS 106 180511-93-7, BILD 1351 211113-85-8 236391-65-4, BILD 1633 236391-66-5, GTI 2040 236391-67-6, GTI 2501 236392-18-0, Endinovere 236392-56-6, OCX 191 236392-75-9, PL 7
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT 56-84-8, L-Aspartic acid, biological studies 56-85-9, L-Glutamine, biological studies 70-47-3, L-Asparagine, biological studies
 RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
 (PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
IT 9040-57-7, Ribonucleotide reductase 9068-38-6, Reverse transcriptase 144114-21-6, Retropepsin
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (inhibitors; PEG-asparaginase, and combinations with other agents, for HIV infection treatment)
RE.CNT 8
RE

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L3 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:113524 HCAPLUS
DN 130:177527
TI Therapeutic process for inhibiting NF-.kappa.B
IN Elford, Howard L.
PA USA
SO PCT Int. Appl., 12 pp.
 CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-7 (Pharmacology)
FAN.CNT 1

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    PATENT NO.      KIND  DATE          APPLICATION NO.  DATE
    --------------- ----  --------      ---------------  --------
PI  WO 9906009       A2   19990211      WO 1998-US15715  19980729
    WO 9906009       A3   19990902
        W: CA, JP
        RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
            PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1997-54230   19970730
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OS MARPAT 130:177527
AB A therapeutic process is provided for the inhibition of NF-.kappa.B in mammals in whose cells NF-.kappa.B has been activated by an agency external to said cell.
ST nuclear factor kappaB inhibitor antiinflammatory
IT Animal virus
 Antitumor agents
 Arteriosclerosis
 Chemotherapy
 Diabetes mellitus
 Oxidizing agents
 Radiotherapy
 Transplant (organ)
 (NF-.kappa.B activation by; therapeutic process for inhibiting NF-.kappa.B)
IT Cytokines
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (NF-.kappa.B activation by; therapeutic process for inhibiting NF-.kappa.B)
IT NF-.kappa.B
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process);

BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; therapeutic process for inhibiting NF-.kappa.B)

IT Anti-inflammatory drugs
Radical scavengers
(therapeutic process for inhibiting NF-.kappa.B)

IT 141440-14-4, Protein kinase B
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(NF-.kappa.B activation by; therapeutic process for inhibiting NF-.kappa.B)

IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; therapeutic process for inhibiting NF-.kappa.B)

IT 69839-83-4, N,3,4-Trihydroxybenzamide 95933-72-5, Amidox 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic process for inhibiting NF-.kappa.B)

L3 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:727246 HCAPLUS
DN 130:90042
TI Characterization of the enzymic activity for biphasic competition by guanoxabenz (1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine) at .alpha.2-adrenoceptors. I. Description of an enzymic activity in spleen membranes
AU Uhlen, Staffan; Dambrova, Maija; Tiger, Gunnar; Oliver, Douglas W.; Wikberg, Jarl E. S.
CS Department of Pharmaceutical Biosciences, Division of Pharmacology, Uppsala University, Uppsala, Swed.
SO Biochem. Pharmacol. (1998), 56(9), 1111-1119
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-2 (Pharmacology)
AB The mechanism for formation of high-affinity binding of 1-(2,6-dichlorobenzylidene-amino)-3-hydroxyguanidine (guanoxabenz) to .alpha.2-adrenoceptors was studied in particulate fractions from the rat spleen. The proportion of apparent high vs. low-affinity .alpha.2-adrenoceptor binding sites increased with increasing incubation time and was also augmented by Mg2+ ions. The formation of high-affinity guanoxabenz binding seemed to be inhibited by a series of N-hydroxyguanidine analogs to guanoxabenz, as well as by a series of metabolic inhibitors that included allopurinol, 1-chloro-2,4-dinitrobenzene, 5,5'-dithiobis-(2-nitrobenzoic acid), cibacron blue, phenyl-p-benzoquinone, didox, and ***trimidox*** . The formation of guanoxabenz high-affinity binding was also inhibited in a time- and concn.-dependent fashion by preincubating the membranes with the LW03 N-hydroxyguanidine analog of guanoxabenz. Moreover, when the spleen membranes were extensively washed for 30 min with buffers at 25.degree., the guanoxabenz high-affinity binding disappeared. However, when these washed membranes were supplemented with xanthine, the apparent affinity of guanoxabenz increased four- to five-fold. Taken together, all data were compatible with the theory that the formation of high-affinity binding was dependent on the generation of a guanoxabenz metabolite that showed an approx. 100-fold greater affinity for the .alpha.2-adrenoceptors than guanoxabenz itself. Because the most potent blocker of the formation of high-affinity binding was allopurinol (apart from some N-hydroxyguanidine analogs to guanoxabenz) and since the activity could be restored with xanthine, a likely candidate responsible for the metabolic activation is xanthine oxidase.
ST guanoxabenz metab spleen adrenoceptor binding; xanthine oxidase guanoxabenz metab adrenoceptor binding

IT Cell membrane
Cerebral cortex
Drug metabolism
(metabolic activation in spleen and cerebral cortex membranes for guanoxabenz binding to .alpha.2A-adrenoceptors)

IT Spleen
(metabolic activation in spleen membranes for guanoxabenz binding to .alpha.2A-adrenoceptors)

IT .alpha.2-Adrenoceptors subtype A
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabolic activation in spleen membranes for guanoxabenz binding to .alpha.2A-adrenoceptors)

IT 9002-17-9, Xanthine oxidase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(metabolic activation in spleen membranes for guanoxabenz binding to .alpha.2A-adrenoceptors)

IT 24047-25-4, Guanoxabenz
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(metabolic activation in spleen membranes for guanoxabenz binding to .alpha.2A-adrenoceptors)

IT 7439-95-4, Magnesium, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(metabolic activation in spleen membranes for guanoxabenz binding to .alpha.2A-adrenoceptors)

RE.CNT 23

RE
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L3 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:487631 HCAPLUS
DN 129:211378
TI Enhanced effects of Adriamycin by combination with a new ribonucleotide reductase inhibitor, ***trimidox*** , in murine leukemia
AU Fritzer-Szekeres, Monika; Novotny, Ladislav; Romanova, Darina; Gobl, Rainer; Sedlak, Jan; Vachalkova, Anna; Rauko, Peter; Elford, Howard L.; Szekeres, Thomas
CS Clinical Institute for Medical and Chemical Laboratory Diagnostics, Vienna, A-1090, Austria
SO Life Sci. (1998), 63(7), 545-552
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Ribonucleotide reductase is the rate limiting enzyme of de novo DNA synthesis; its activity is significantly increased in tumor cells related to the proliferation rate. Therefore the enzyme is considered to be an excellent target for cancer chemotherapy. In the present study we tested the in vitro and in vivo antitumor effects of a drug combination using ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a novel inhibitor of ribonucleotide reductase with adriamycin, a widely used anticancer drug. This combination was selected because adriamycin generates free radicals being responsible for cardiotoxic side effects, ***trimidox*** has been shown to be a good free radical scavenger. The in vitro cytotoxic effect of the drug combination was examd. in L1210 mouse leukemia cells employing a MTT chemosensitivity assay. Incubation of these cells with adriamycin and ***trimidox*** together yielded less than additive cytotoxic effects compared to either drug alone. These effects were not caused by the involvement of p-glycoprotein mediated drug efflux. However, when the effect of ***trimidox*** and adriamycin in combination was examd. in L1210 leukemia bearing mice antitumor effects of adriamycin could be enhanced by the presence of ***trimidox*** . Our data indicate, that the in vivo combination of adriamycin together with ***trimidox*** might be beneficial for the treatment of malignancies.
ST ***trimidox*** Adriamycin leukemia inhibition

IT Drug transport
(P-glycoprotein-mediated; enhanced effects of Adriamycin by combination with a new ribonucleotide reductase inhibitor, ***trimidox*** , in murine leukemia)

IT Leukemia inhibitors
Synergistic drug interactions
(enhanced effects of Adriamycin by combination with a new ribonucleotide reductase inhibitor, ***trimidox*** , in murine leukemia)

IT 25316-40-9, Adriamycin 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced effects of Adriamycin by combination with a new ribonucleotide reductase inhibitor, ***trimidox*** , in murine leukemia)

IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enhanced effects of Adriamycin by combination with a new ribonucleotide reductase inhibitor, ***trimidox*** , in murine leukemia)

L3 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:429154 HCAPLUS
DN 129:170304
TI ***Trimidox*** -mediated morphological changes during erythroid differentiation is associated with the stimulation of hemoglobin and

F-cell production in human K562 cells
AU Iyamu, Efe W.; Adunyah, Samuel E.; Elford, Howard L.; Fasold, Hugo; Turner, Ernest A.
CS Comprehensive Sickle Cell Center, Nashville, TN, 37208, USA
SO Biochem. Biophys. Res. Commun. (1998), 247(3), 759-764
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
CC 1-6 (Pharmacology)
AB ***Trimidox*** (3,4,5-trihydroxybenzamidoxime) has been shown to reduce the activity of ribonucleotide reductase with accompanied growth inhibition and differentiation of mammalian cells. Hydroxyurea (HU) is the only ribonucleotide reductase inhibitor in clin. use for the treatment and management of sickle cell anemia, since this compd. increases fetal Hb (Hb F) prodn.: a potent inhibitor of sickle Hb (Hb,SS) polymn. However, the main limitations of HU is its lack of potency, myelosuppression and short half life. These studies investigated the effects of ***trimidox*** on the induction of Hb and F-cells prodn. in K562 erythroleukemia cells. Our study reveals that ***trimidox*** exhibits concn. dependent inhibitory effect on K562 cells with increase in benzidine pos. normoblasts and F-cells prodn. as well as morphol. changes typical of erythroid differentiation. These findings provide the first evidence that the growth inhibitory differentiation of cells induced by ***trimidox*** enhance Hb and F-cells prodn. (c) 1998 Academic Press.
ST ***trimidox*** fetal Hb ribonucleotide reductase; sickle Hb ***trimidox*** ribonucleotide reductase inhibition
IT Erythrocyte
(differentiation; ***trimidox*** -mediated morphol. changes during erythroid differentiation is assocd. with the stimulation of Hb and F-cell prodn. in human K562 cells)
IT Sickle cell anemia
(***trimidox*** -mediated morphol. changes during erythroid differentiation is assocd. with the stimulation of Hb and F-cell prodn. in human K562 cells)
IT 95933-74-7, ***Trimidox***
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(***trimidox*** -mediated morphol. changes during erythroid differentiation is assocd. with the stimulation of Hb and F-cell prodn. in human K562 cells)
IT 9034-63-3, Hemoglobin F 9040-57-7, Ribonucleotide reductase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(***trimidox*** -mediated morphol. changes during erythroid differentiation is assocd. with the stimulation of Hb and F-cell prodn. in human K562 cells)

L3 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:415518 HCAPLUS
DN 129:156586
TI Interaction of gallium nitrate with other inhibitors of ribonucleotide reductase: effects on the proliferation of human leukemic cells
AU Myette, Michael S.; Elford, Howard L.; Chitambar, Christopher R.
CS Division of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SO Cancer Lett. (Shannon, Irel.) (1998), 129(2), 199-204
CODEN: CALEDQ; ISSN: 0304-3835
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Ribonucleotide reductase, a key enzyme in deoxyribonucleotide synthesis, is an important target for cancer chemotherapy. Drugs that inhibit its individual components may act synergistically to block DNA synthesis. Prior work has established that gallium inhibits the R2 subunit of ribonucleotide reductase. We show that gallium acts synergistically with the ribonucleotide reductase inhibitors gemcitabine and hydroxyurea to inhibit the proliferation of CCRF-CEM cells. In contrast, combinations of gallium with the ribonucleotide reductase inhibitors amidox, didox, or ***trimidox*** produced antagonistic effects on cell growth. Spectroscopy anal. revealed that as a result of their metal-binding properties, amidox, didox and ***trimidox*** formed complexes with gallium, thus negating potential synergistic actions. Our results have important implications in the design of clin. trials using these ribonucleotide reductase inhibitors in combination.
ST ribonucleotide reductase inhibitor gallium leukemia
IT DNA formation
Leukemia inhibitors
Synergistic drug interactions
(interaction of gallium nitrate with other inhibitors of ribonucleotide reductase and effects on proliferation of human leukemic cells)
IT 127-07-1, Hydroxyurea 13494-90-1, Gallium nitrate 69839-83-4, Didox 95058-81-4, Gemcitabine 95933-72-5, Amidox 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interaction of gallium nitrate with other inhibitors of ribonucleotide reductase and effects on proliferation of human leukemic cells)
IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interaction of gallium nitrate with other inhibitors of ribonucleotide reductase and effects on proliferation of human leukemic cells)

L3 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:49701 HCAPLUS
DN 128:169555
TI DNA-protective activity of new ribonucleotide reductase inhibitors
AU Rauko, Peter; Romanova, Darina; Miadokova, Eva; Macakova, Kvetoslava; Novotny, Ladislav; Elford, Howard L.; Szekeres, Thomas
CS Department of Experimental Therapy, Cancer Research Institute, Slovak Academy of Sciences, Bratislava, SK-81232, Slovakia
SO Anticancer Res. (1997), 17(5A), 3437-3440
CODEN: ANTRD4; ISSN: 0250-7005
PB Anticancer Research
DT Journal
LA English
CC 1-12 (Pharmacology)
AB The DNA-protective activity of hydroxyurea (HU) and novel ribonucleotide reductase (RR) inhibitors amidox (AX), didox (DX) and ***trimidox*** (TX) was examd. using hydrogen peroxide as the DNA-damaging agent. The exposure of superspiralized plasmid DNA mols. (pBR 322) to H2O2 under precisely defined in vitro conditions initiates a change in DNA topol. (DNA form I relaxes to DNA form II). This electrophoretically monitored change in the plasmid DNA topol. is related to the induction of ss-DNA breaks and corresponds with DNA exposition to free radicals. The inhibition of DNA relaxation (the prevention of DNA damage induced by hydrogen peroxide) depended on the free radical scavenging capacity of the drugs investigated. HU exerted DNA protective activity at a concn. of 4 mM, AX at concn. of 1 .mu.M, TX at a concn. of 5 .mu.M and DX at a concn. of 25 .mu.M (the free radical scavenging activity increases from HU to AX in following manner: HU .mchlt. DX < TX < AX). It can be concluded that the new synthetic RR-inhibitor AX which is being investigated at the preclin. level as a potential anti-cancer drug possess the highest capacity for scavenging of free radicals.
ST DNA protection ribonucleotide reductase inhibitor; radical scavenging ribonucleotide reductase inhibitor DNA
IT DNA damage
Radical scavengers
(DNA-protective activity of new ribonucleotide reductase inhibitors and hydroxyurea in relation to radical scavenging capacity)
IT 7722-84-1, Hydrogen peroxide, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(DNA-protective activity of new ribonucleotide reductase inhibitors and hydroxyurea in relation to radical scavenging capacity)
IT 127-07-1, Hydroxyurea 69839-83-4, Didox 95933-72-5, Amidox
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA-protective activity of new ribonucleotide reductase inhibitors and hydroxyurea in relation to radical scavenging capacity)
IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; DNA-protective activity of new ribonucleotide reductase inhibitors and hydroxyurea in relation to radical scavenging capacity)

L3 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:26676 HCAPLUS
DN 128:136198
TI Enhanced effects of adriamycin by combination with a new ribonucleotide reductase inhibitor, ***trimidox*** , in murine leukemia
AU Novotny, L.; Romanova, D.; Gobl, R.; Sedlak, J.; Vachalkova, A.; Rauko, P.; Fritzer-Szekeres, M.; Elford, H. L.; Szekeres, T.
CS Cancer Research Inst., SAS, Bratislava, SK-812 32, Slovakia
SO Haematol. Blood Transfus. (1998), 39(Acute Leukemias VII), 556-561
CODEN: HBTRDV; ISSN: 0171-7111
PB Springer-Verlag
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Ribonucleotide reductase is the rate limiting enzyme of de novo DNA synthesis; its activity is significantly increased in tumor cells related to the proliferation rate of the tumor cell. Therefore the enzyme is considered to be an excellent target for cancer chemotherapy. In the present study we tested the in vitro and in vivo antitumor effects of a drug combination using ***trimidox*** (3,4,5-trihydroxybenzohydroxamidoxime), a novel inhibitor of ribonucleotide reductase with adriamycin, a widely used anticancer drug. This combination was selected because adriamycin generates free radicals, which are responsible for cardiotoxic side effects of adriamycin treatment, and because ***trimidox*** has been shown to be a good free radical scavenger. The in vitro cytotoxic effect of the drug combination was examd. in L 1210 mouse leukemia cells employing an MTT chemo-sensitivity assay. Simultaneous in vitro incubation of these cells yielded antagonistic cytotoxic effects compared to either drug alone. These effects were not caused by the involvement of p-glycoprotein mediated drug efflux. However, when the effect of ***trimidox*** and adriamycin in combination was examd. in L 1210 leukemia bearing mice, antitumor effects of adriamycin could be enhanced by the presence of ***trimidox*** . Animals were treated on day two after tumor cell injection with 5 mg/kg

→ aug. 4th

adriamycin and received 250 mg/kg ***trimidox*** on days 2,3 and 4. Mice treated with adriamycin or ***trimidox*** alone yielded a 41 and 31% increase in life span, resp. However, animals, which were treated with both drugs, showed a 83% increase of their life span. Our data indicate, that in vitro results of drug combinations should be interpreted with extreme caution and suggest that the in vivo combination of adriamycin together with ***trimidox*** might be beneficial for the treatment of malignancies.
ST adriamycin leukemia ***trimidox*** P glycoprotein
IT Drug interactions
Leukemia inhibitors
(adriamycin antileukemic effects enhancement by ribonucleotide reductase inhibitor ***trimidox***)
IT P-glycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(adriamycin antileukemic effects enhancement by ribonucleotide reductase inhibitor ***trimidox***)
IT 25316-40-9, Adriamycin 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adriamycin antileukemic effects enhancement by ribonucleotide reductase inhibitor ***trimidox***)

L3 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:795554 HCAPLUS
DN 128:123476
TI Effective use of ribonucleotide reductase inhibitors (didox and ***trimidox***) alone or in combination with didanosine (ddI) to suppress disease progression and increase survival in murine acquired immunodeficiency syndrome (MAIDS)
AU Mayhew, Christopher; Oakley, Oliver; Piper, James; Hughes, Nedda K.; Phillips, Jonathan; Birch, Nicholas J.; Elford, Howard L.; Gallicchio, Vincent S.
CS Laboratory of Experimental Immunohematopoiesis and Developmental Therapeutics, Departments of Clinical Sciences and Internal Medicine, Chandler Medical Center, University of Kentucky, Lexington, KY, 40536, USA
SO Cell. Mol. Biol. (Paris) (1997), 43(7), 1019-1029
CODEN: CMOBEF; ISSN: 0145-5680
PB C.M.B. Association
DT Journal
LA English
CC 1-5 (Pharmacology)
AB Ribonucleotide reductase inhibitors (RRIs) have been recently shown to inhibit retroviral replication. We examd. a new series of RRIs, 3,4-dihydroxybenzohydroxamic acid (Didox) and 3,4,5-trihydroxybenzohydroxamidoxime (***Trimidox***) for their ability to alter disease progression in murine acquired immunodeficiency syndrome (MAIDS), both alone and in combination with 2',3'-dideoxyinosine (ddI). MAIDS disease was induced by inoculation of female C57BL/6 mice with the LP-BM5 murine leukemia virus (MuLV) and disease progression characterized by extensive peripheral lymphadenopathy and splenomegaly. Efficacy of treatment with these drugs was based upon their ability to influence survival and disease pathophysiol. by monitoring the development of splenomegaly. Toxicity was detd. by changes in body wt., total peripheral white blood cell count and hematocrit. Didox or ***trimidox*** monotherapy was assocd. with increased survival and decreased disease pathophysiol., with no apparent toxicity. Combined with ddI, their ability to reduce development of viral induced splenomegaly was enhanced compared to ***trimidox*** , didox or ddI alone. These results demonstrate RRIs have potent activity in reversing the disease manifestations characteristic of MAIDS. Further studies are warranted to det. human clin. efficacy.
ST ribonucleotide reductase inhibitor didanosine murine AIDS; antiviral didox ***trimidox*** didanosine AIDS HIV1
IT AIDS (disease)
Antiviral agents
Drug interactions
Human immunodeficiency virus 1
(ribonucleotide reductase inhibitors (didox and ***trimidox***) alone or in combination with didanosine: suppression of MAIDS)
IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; ribonucleotide reductase inhibitors (didox and ***trimidox***) alone or in combination with didanosine: suppression of MAIDS)
IT 69655-05-6, Didanosine 69839-83-4, Didox 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ribonucleotide reductase inhibitors (didox and ***trimidox***) alone or in combination with didanosine: suppression of MAIDS)

L3 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:567538 HCAPLUS
DN 127:243220
TI Selective inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by novel antioxidant compounds
AU Lee, Raymond; Beauparlant, Pierre; Elford, Howard; Ponka, Premysl; Hiscott, John
CS Lady Davis Institute for Medical Research, McGill University, Montreal, PQ, H3T 1E2, Can.
SO Virology (1997), 234(2), 277-290
CODEN: VIRLAX; ISSN: 0042-6822
PB Academic
DT Journal
LA English
CC 1-12 (Pharmacology)
AB Oxidative stress activates the NF-.kappa.B/Rel transcription factors which are involved in the activation of numerous immunoregulatory genes and the human immunodeficiency virus type 1 (HIV-1) long terminal repeat (LTR). In the present study, we examd. the effects of established and novel compds. including antioxidants, ribonucleotide reductase inhibitors, and iron chelators on NF-.kappa.B activation and HIV LTR-mediated gene expression induced by TNF-.alpha.. N-Acetylcysteine (NAC), pyrrolidinedithiocarbamate (PDTC), and ***Trimidox*** (TD) at various concns. inhibited TNF-.alpha.-induced NF-.kappa.B binding in Jurkat cells. Pretreatment of cells with these compds. prior to stimulation prevented I.kappa.B.alpha. degrdn. Phosphorylation of I.kappa.B.alpha., a prerequisite for its signal-induced degrdn., was abrogated in these cells, indicating that oxidative stress is an essential step in the NF-.kappa.B activation pathway. On the other hand, iron chelators desferrioxamine, pyridoxal isonicotinoyl hydrazone (PIH), and salicylaldehyde isonicotinoyl hydrazone (SIH) showed no inhibition of TNF-.alpha.-induced NF-.kappa.B DNA-binding activity. Synergistic induction of HIV-1 LTR-mediated gene expression by TNF-.alpha. and the HIV-1 transactivator Tat in Jurkat cells was significantly suppressed in the presence of NAC and TD, but not PDTC. The inhibition of NAC and TD on LTR-directed gene expression was diminished when NF-.kappa.B-binding sites in the LTR were deleted, indicating that these compds. affected the NF-.kappa.B component of the synergism. Iron chelators PIH and SIH also showed some inhibitory effect on LTR-mediated gene activation, presumably through an NF-.kappa.B-independent mechanism. These expts. demonstrate that TD, at concn. 50 times lower than the effective concn. of NAC, potently inhibits NF-.kappa.B activity and suppresses HIV LTR expression.
ST antioxidant NFkB HIV1 gene
IT Antioxidants (pharmaceutical)
Human immunodeficiency virus 1
(inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by antioxidants)
IT Tumor necrosis factor .alpha.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by antioxidants)
IT LTR (long terminal repeat)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by antioxidants)
IT NF-.kappa.B
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by antioxidants)
IT Chelating agents
(iron; inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by antioxidants)
IT 70-51-9, Desferrioxamine 495-84-1, Salicylaldehyde isonicotinoyl hydrazone 616-91-1, N-Acetylcysteine 737-86-0, Pyridoxal isonicotinoyl hydrazone 25769-03-3, 1-Pyrrolidinecarbodithioic acid 69839-83-4, Didox 95933-72-5, Amidox 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibition of I.kappa.B.alpha. phosphorylation and HIV-1 LTR-directed gene expression by antioxidants)

L3 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:529356 HCAPLUS
DN 127:130355
TI The effect of new combinations of antimetabolites and ***trimidox*** on cancer cells
AU Romanova, D.; Raslova, H.; Plaschke, K.; Novotny, L.; Fritzer, M.
CS Ustav experimentalnej onkologie, Bratislava, 812 32, Slovakia
SO Farm. Obz. (1995), 64(7-8), 180-187
CODEN: FAOBAS; ISSN: 0014-8172
PB Zdravotnicke Vydavatelstvo HERBA
DT Journal; General Review
LA Slovak
CC 1-0 (Pharmacology)
AB A review with 22 refs. The effects of ***trimidox*** , a new inhibitor of ribonucleotide reductase, used in combination with antimetabolites arabinosylcytosine (ara-C) and gemcitabine (difluorodideoxycytidine) used in anticancer chemotherapy were studied in vitro cultures of human colon cancer HT-29 cells. The effects ***trimidox*** were compared with the effects of thiazofurine combined with hypoxanthine or allopurinol. The cytostatic effects were also evaluated in human leukemic cells HL-60. The levels of ribonucleoside and deoxyribonucleoside triphosphates and cell cycle responses were detd. The mechanisms of ***trimidox*** action, biochem. pathways, anticancer activity, synergism, and cytotoxicity are discussed.
ST review ***trimidox*** antitumor combination araC gemcytabine
IT Antitumor agents
Drug interactions

HL-60 cell
HT-29 cell
(antitumor effect of ***trimidox*** in combination of antimetabolites in cancer cells)

IT 68-94-0, Hypoxanthine 127-07-1, Hydroxyurea 147-94-4, Ara-c 315-30-0, Allopurinol 60084-10-8, Tiazofurin 69839-83-4, Didox 95058-81-4, Gemcitabine 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor effect of ***trimidox*** in combination of antimetabolites in cancer cells)

L3 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:499518 HCAPLUS
DN 127:135517
TI Genotoxic properties of the newly synthesized antineoplastic agents amidox, didox, and ***trimidox***
AU Miadokova, E.; Macakova, K.; Podstavkova, S.; Vlcek, D.
CS Department Genetics, Faculty Sciences, Bratislava, 84215, Slovakia
SO Pharmazie (1997), 52(7), 540-544
CODEN: PHARAT; ISSN: 0031-7144
PB Govi-Verlag Pharmazeutischer Verlag
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 4
AB Toxic and genotoxic effects of 3 polyhydroxy-substituted benzohydroxamates (amidox, didox, and ***trimidox***), having antineoplastic activities by the mechanism of the ribonucleotide reductase activity inhibition, were evaluated by reverse mutation assay on Salmonella typhimurium strains TA97, TA98, TA100, TA102. While amidox did not exert any toxic effect, didox, and ***trimidox*** were toxic. The toxicity of the test chems. was dependent on the structure of their mol. and the repair capacity of the test strains. ***Trimidox*** exhibited the highest toxicity, and it was proved as a direct-acting frameshift mutagen. Its mutagenic effect was increased after a metabolic activation. Amidox and didox can be classified as frameshift promutagens.
ST antineoplastic agent amidox didox ***trimidox*** genotoxicity
IT Frameshift mutation
(genotoxicity of antineoplastic agent ***trimidox*** caused by)
IT Antitumor agents
(genotoxicity of antineoplastic agents amidox, didox, and ***trimidox***)
IT Genotoxicity
Toxicity
(of antineoplastic agents amidox, didox, and ***trimidox***)
IT 69839-83-4, Didox 95933-72-5, Amidox 95933-74-7, ***Trimidox***
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(genotoxicity of antineoplastic agents)
IT 9047-64-7
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(genotoxicity of antineoplastic agents amidox, didox, and ***trimidox*** caused by inhibition of)

L3 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:327317 HCAPLUS
DN 127:39615
TI The new inhibitors of ribonucleotide reductase. Comparison of some physicochemical properties
AU Romanova, Darina; Vachalkova, Anna; Szekeres, Thomas; Elford, Howard L.; Novotny, Ladislav
CS Cancer Res. Inst. Slovak Academy Sci., Bratislava, SK-81232, Slovakia
SO J. Pharm. Biomed. Anal. (1997), 15(7), 951-956
CODEN: JPBADA; ISSN: 0731-7085
PB Elsevier
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 22
AB Amidox (AX), didox (DX) and ***trimidox*** (TX), compds. synthesized as new ribonucleotide reductase inhibitors, have been investigated by UV spectrophotometry, polarog. HPLC. The expts. were performed at various pH values. The changes in UV absorption of the compds. studied were recorded and it was demonstrated that these changes are related to the pH and to structural features of the investigated mols. Only amidox and ***trimidox*** were reduced during polarog. expts. in Britton-Robinson buffer. The redn. of both compds. proceeded in 2 1-electron steps in acid solns. One 2-electron diffuse irreversible wave was obsd. at basic pH values. The values of the half-wave potential became more neg. with increasing pH values. HPLC assay also showed changes in the retention of compds. investigated, particularly when the pH of the mobile phase was close to the dissocn. const. of the particular drug. The changes of physicochem. properties detected by the methods are related to different chem. structures (the most significant changes were obsd. in alk. pH).
ST ribonucleotide reductase inhibitor physicochem property; polarog ribonucleotide reductase inhibitor; UV spectrometry ribonucleotide reductase inhibitor
IT Electrochemical reduction
UV and visible spectroscopy
(physicochem. properties of ribonucleotide reductase inhibitors)
IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(physicochem. properties of ribonucleotide reductase inhibitors)
IT 69839-83-4, Didox 95933-72-5, Amidox 95933-74-7, ***Trimidox***
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(physicochem. properties of ribonucleotide reductase inhibitors)

L3 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:1007345 HCAPLUS
DN 124:75813
TI Iron binding capacity of ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a new inhibitor of the enzyme ribonucleotide reductase
AU Szekeres, Thomas; Vielnascher, Elisabeth; Novotny, Ladislav; Vachalkova, Anna; Fritzer, Monika; Findenig, Gabriele; Goebl, Rainer; Elford, Howard L.; Goldenberg, Hans
CS Inst. Medizinsche Chemie, Univ. Wien, Vienna, Austria
SO Eur. J. Clin. Chem. Clin. Biochem. (1995), 33(11), 785-9
CODEN: EJCBEO; ISSN: 0939-4974
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Ribonucleotide reductase is the rate limiting enzyme of deoxynucleoside triphosphate synthesis and is considered to be an excellent target of cancer chemotherapy. ***Trimidox*** , a newly synthesized compd., inhibits this enzyme and has in vitro and in vivo antitumor activity. As ***trimidox*** was able to upregulate the expression of the transferrin receptor in HL-60 human promyelocytic leukemia cells, the authors have now investigated the capability of ***trimidox*** to interfere with iron metab. The authors show by photometric and polarog. methods that ***trimidox*** is able to form an iron complex. However, its cytotoxic action cannot be circumvented by addn. of iron-satd. transferrin or iron-ammonium citrate, indicating that the iron complexing capacity is not responsible for the mechanism of action of this compd. When HL-60, K562 or L1210 leukemia cells were incubated with the ***trimidox*** -iron complex itself, the authors could observe increases of the 50% growth inhibitory capacity of the complex in comparison with ***trimidox*** alone. The authors conclude that ***trimidox*** is able to form an iron complex, but in contrast to other agents, the anticancer activity cannot be contributed to this effect alone. Further studies will have to elucidate the mol. mechanism of action of this new and promising anticancer agent.
ST iron ***trimidox*** complex ribonucleotide reductase antitumor
IT Neoplasm inhibitors
(iron binding capacity of ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a new inhibitor of the enzyme ribonucleotide reductase)
IT 9068-66-0, Ribonucleotide reductase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibitor; iron binding capacity of ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a new inhibitor of the enzyme ribonucleotide reductase)
IT 1185-57-5D, Ferric ammonium citrate, ***trimidox*** complex
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(iron binding capacity of ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a new inhibitor of the enzyme ribonucleotide reductase)
IT 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iron binding capacity of ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a new inhibitor of the enzyme ribonucleotide reductase)
IT 7439-89-6, Iron, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(iron binding capacity of ***trimidox*** (3,4,5-trihydroxybenzamidoxime), a new inhibitor of the enzyme ribonucleotide reductase)

L3 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:982076 HCAPLUS
DN 124:134431
TI Ribonucleotide reductase as target for enzyme-directed chemotherapy. Effects of ***trimidox*** (3,4,5-trihydroxybenzohydroxamidoxime), a new inhibitor of ribonucleotide reductase
AU Findenig, G.; Vielnascher, E.; Goebl, R.; Fritzer-Szekeres, M.; Szekeres, T.
CS Inst. Med. Chem., Univ. Wien, Vienna, A-1090, Austria
SO Wien. Klin. Wochenschr. (1995), 107(22), 694-7
CODEN: WKWOAO; ISSN: 0043-5325
DT Journal; General Review
LA German
CC 1-0 (Pharmacology)
Section cross-reference(s): 7
AB A review with 28 refs. describing the biochem., morphol., and cytotoxic effects of ***trimidox*** and other polyhydroxy-substituted benzohydroxamate derivs. on leukemia cell lines. Selection criteria,

effects, and combinations used in enzyme-targeted chemotherapy are described for these ribonucleotide reductase inhibitors.
ST Review benzohydroxamide cancer chemotherapy; ***trimidox*** biochem cytotoxic effect leukemia review; ribonucleotide reductase inhibitor ***trimidox*** review
IT Neoplasm inhibitors
(ribonucleotide reductase as target for enzyme-directed chemotherapy)
IT 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ribonucleotide reductase as target for enzyme-directed chemotherapy)
IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ribonucleotide reductase as target for enzyme-directed chemotherapy)

L3 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:270272 HCAPLUS
DN 122:45904
TI Synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells
AU Szekeres, Thomas; Fritzer, Monika; Strobl, Herbert; Gharehbaghi, Kamran; Findenig, Gabriele; Elford, Howard L.; Lhotka, Christian; Schoen, Hans J.; Jayaram, Hiremagalur N.
CS Inst. Med. Chem., Univ. Vienna Med. Sch., Vienna, Austria
SO Blood (1994), 84(12), 4316-21
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Increased ribonucleotide reductase (RR) activity has been linked with malignant transformation and tumor cell growth. Therefore, this enzyme is considered to be an excellent target for cancer chemotherapy. The authors have examd. the effects of a newly patented RR inhibitor, ***trimidox*** (3,4,5-trihydroxybenzohydroxamidoxime). ***Trimidox*** inhibited the growth of human promyelocytic leukemia HL-60 cells with an IC50 of 35 .mu.mol/L. Incubation of HL-60 cells with 50 .mu.mol/L ***trimidox*** for 24 h decreased deoxyguanosine triphosphate (dGTP) and deoxycytidine triphosphate (dCTP) pools to 24% and 39% of control values, resp. Incubation of HL-60 cells with 20 to 80 .mu.mol/L ***trimidox*** even up to a period of 4 days did not alter the distribution of cells in different phases of cell cycle. Sequential incubation of HL-60 cells with ***trimidox*** (25 .mu.mol/L) for 24 h and then with 10 .mu.mol/L tiazofurin (an inhibitor of inosine monophosphate dehydrogenase) for 4 days produced synergistic growth inhibitory activity, and the cell no. decreased to 16% of untreated controls. When differentiation-linked cell surface marker expressions were detd. in cells treated with ***trimidox*** and tiazofurin, a significantly increased fluorescence intensity was obsd. for the CD 11b (2.9-fold), CD 33 (1.9-fold), and HLA-D cell surface antigens. Expression of the transferrin receptor (CD71) increased 7.3-fold in cells treated with both agents, compared with untreated controls. The results suggest that ***trimidox*** in combination with tiazofurin might be useful in the treatment of leukemia.
ST promyelocytic leukemia inhibitor ***trimidox*** tiazofurin synergism
IT Transferrin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells)
IT Neoplasm inhibitors
(promyelocytic leukemia, synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells)
IT Drug interactions
(synergistic, synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transferrin, synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells)
IT 60084-10-8, Tiazofurin 95933-74-7, ***Trimidox***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells)
IT 9040-57-7, Ribonucleotide reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synergistic growth inhibitory and differentiating effects of ***trimidox*** and tiazofurin in human promyelocytic leukemia HL-60 cells)

L3 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:79317 HCAPLUS
DN 123:102138
TI Synergistic cytotoxic effects of chemotherapeutic drugs on colon tumor cells by simultaneous inhibition of de novo and salvage metabolic pathways
AU Szekeres, T.; Fritzer, M.; Schoen, H. J.; Findenig, G.; Lhotka, C.
CS Inst. Med. Chem., Univ. Wien, Vienna, A-1090, Austria
SO Wien. Klin. Wochenschr. (1994), 106(14), 459-63
CODEN: WKWOAO; ISSN: 0043-5325
DT Journal
LA German
CC 1-6 (Pharmacology)
AB The cytotoxic effect (CE) of various drug combinations was evaluated with the human tumor cell line HT-29. ***Trimidox*** was combined with Ara-C or 2',2'-difluoro-deoxycytidine (DFDC). Synergistic CEs were obsd. Colony no. decreased to 71-73% of the calcd. additive cytotoxicity by sequential treatment with ***trimidox*** and Ara-C, or by simultaneous treatment with ***trimidox*** and DFDC. The combination of tiazofurin with allopurinol led to inhibition of hypoxanthine-guanine phosphoribosyl transferase and synergistic CE. Thus, colony no. decreased to 69 and 37% of the calcd. additive cytotoxicity.
ST cancer chemotherapy colon tumor cell
IT Drug interactions
(synergistic cytotoxic effects of chemotherapeutic drugs on colon tumor cells)
IT Neoplasm inhibitors
(colon, synergistic cytotoxic effects of chemotherapeutic drugs on colon tumor cells)
IT Intestine, neoplasm
(colon, inhibitors, synergistic cytotoxic effects of chemotherapeutic drugs on colon tumor cells)
IT 9016-12-0, Hypoxanthine-guanine phosphoribosyl transferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in synergistic cytotoxic effects of chemotherapeutic drugs on colon tumor cells)
IT 68-94-0, Hypoxanthine 147-94-4, Ara-C 315-30-0, Allopurinol 60084-10-8, Tiazofurin 95933-74-7, ***Trimidox*** 103882-84-4, 2',2'-Difluorodeoxycytidine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic cytotoxic effects of chemotherapeutic drugs on colon tumor cells)

L3 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:569910 HCAPLUS
DN 121:169910
TI Biochemical and antitumor activity of ***trimidox*** , a new inhibitor of ribonucleotide reductase
AU Szekeres, Thomas; Gharehbaghi, Kamran; Fritzer, Monika; Woody, Michael; Srivastava, Arun; van't Riet, Bart; Jayaram, Hiremagalur N.; Elford, Howard L.
CS Inst. Med. Chem., Univ. Vienna, Austria
SO Cancer Chemother. Pharmacol. (1994), 34(1), 63-6
CODEN: CCPHDZ; ISSN: 0344-5704
DT Journal
LA English
CC 1-6 (Pharmacology)
AB ***Trimidox*** (3,4,5-trihydroxybenzamidoxime), a newly synthesized analog of didox (N,3,4-trihydroxybenzamide) reduced the activity of ribonucleotide reductase (EC 1.17.4.1) in exts. of L1210 cells with an IC50 of 5 .mu.M, whereas hydroxyurea, the only ribonucleotide reductase inhibitor in clin. use, exhibited an IC50 of 500 .mu.M. Ribonucleotide reductase activity was also measured in situ by incubating L1210 cells for 24 h with ***trimidox*** at 7.5 .mu.M (a concn. that inhibited cell proliferation by 50%) or at 100 .mu.M for 2 h; these concns. resulted in a decrease in enzyme activity to 22% and 50%, resp., of the control value. ***Trimidox*** and hydroxyurea were cytotoxic to L1210 cells, with IC50 values of 7.5 and 50 .mu.M, resp. Vs. ribonucleotide reductase, ***trimidox*** and hydroxyurea had IC50 values of 12 and 87 .mu.M, resp. ***Trimidox*** concn.-dependently increased the life span of mice bearing L1210 leukemia. The antitumor activity appeared more pronounced in female mice than in male mice. These findings suggest that ***trimidox*** is a new and potent inhibitor of ribonucleotide reductase and that it is a promising candidate for the chemotherapy of cancer in humans.
ST ***trimidox*** antitumor ribonucleotide reductase
IT Neoplasm inhibitors
(***trimidox*** as, ribonucleotide reductase inhibition in relation to)
IT 127-07-1, Hydroxyurea 69839-83-4, Didox 95933-74-7, ***Trimidox***
(ribonucleotide reductase- and neoplasm-inhibiting activities of)
IT 9040-57-7
(***trimidox*** inhibition of, neoplasm inhibition in relation to)

L3 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:182829 HCAPLUS
DN 118:182829
TI Prevention of activation of HIV-1 by antiviral agents in OM-10.1 cells
AU Feorino, P. M.; Butera, S. T.; Folks, T. M.; Schinazi, R. F.
CS Sch. Med., Emory Univ., Atlanta, GA, 30322, USA
SO Antiviral Chem. Chemother. (1993), 4(1), 55-63
CODEN: ACCHEH; ISSN: 0956-3202
DT Journal
LA English
CC 1-5 (Pharmacology)
AB The development of a reliable and simple system for evaluating compds.

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    that could prevent activation of latent HIV would allow us to devise new
    therapeutic approaches.  These compds. could eventually be used in
    combination with drugs that are effective against acute and chronic
    infections.  The OM-10.1 cell line is a chronically infected clone which
    remains CD4+ until HIV-1 activation with tumor necrosis factor-.alpha..  A
    variety of compds. are known to have antiviral properties against either
    acutely or chronically infected cells were evaluated for their ability to
    inhibit HIV induced expression in these cells.  The authors also examd.
    the effect of several compds. that interact with biochem. pathways that
    may interfere with or enhance the reactivation process.  These included
    nucleoside analogs, cytokines, steroidal and non-steroidal
    anti-inflammatory agents, polyoxometalates, a TAT inhibitor, various
    natural products (including nerve growth factor, N-acetyl-L-cysteine,
    taxol, and interferons), TIBO, porphyrins, and various oligomers.  CD4
    cellular expression and supernatant reverse transcriptase activity were
    quantitated as markers of induced viral expression.  Among several compds.
    evaluated, 3'-fluoro-3'-deoxythymidine (FLT), interferon .gamma., Ro
    5-3335 (a TAT inhibitor) and desferrioxamine were modest and selective
    inhibitors of HIV-1 activation.
ST  antiviral HIV1 activation inhibition; immunodeficiency virus activation
    antiviral
IT  Virucides and Virustats
    Interferons
      (HIV-1 activation prevention by)
IT  Virus, animal
      (human immunodeficiency 1, activation of, antiviral agents in
      prevention of)
IT  50-24-8, Prednisolone   50-78-2, Aspirin   53-43-0, Dehydroepiandrosterone
    53-86-1, Indomethacin   61-68-7, Mefenamic acid   70-51-9, Desferrioxamine
    127-07-1, Hydroxyurea   616-91-1, N-Acetyl-L-cysteine   651-48-9
    3056-17-5, 2',3'-Didehydro-3'-deoxythymidine   4428-95-9   7481-89-2,
    2',3'-Dideoxycytidine   9061-61-4, Nerve growth factor   15687-27-1,
    Ibuprofen   25526-93-6, 3'-Fluoro-3'-deoxythymidine   25609-92-1
    25609-92-1D, thiolated   28507-02-0   28802-05-3   30195-30-3, Ro 5-3335
    30516-87-1, 3'-Azido-3'-deoxythymidine   30811-80-4   33069-62-4, Taxol
    33369-31-2, Zomepirac   35218-75-8   35711-34-3, Tolectin   36322-90-4,
    Piroxicam   38194-50-2, Sulindac   41107-56-6, 3'-Fluoro-2',3'-
    dideoxyuridine   51246-79-8, 3'-Fluoro-2',3'-dideoxycytidine   69655-05-6,
    2',3'-Dideoxyinosine   69839-83-4, Didox   81777-50-6   84472-85-5, CS-87
    87190-79-2, CS-92   89899-81-0, HPA-23   92739-63-4   95933-74-7,
     ***Trimidox***    115249-95-1, 3'-Fluoro-2',3'-dideoxy-5-methylcytidine
    120947-28-6, GLQ 223   123027-56-5   126320-77-2, R-82150   132885-30-4
    136632-04-7   136632-06-9   136632-07-0   136891-12-8, BCH 189
    142168-25-0   142168-26-1   143491-54-7   143823-92-1, JM 2820
      (HIV-1 activation prevention by)


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